Office Action Summary	Application No.	Applicant(s)	
	10/563,818	SUEMATSU ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25-28,30 and 32-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *23,25-28,30 and 32-35* is/are allowed.

6)☒ Claim(s) *36 and 37* is/are rejected.

7)☒ Claim(s) *36 and 37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *1/29/2010* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed November 13, 2009. Claims 23, 25-28, 30 and 32-37 were previously pending. Applicants amended claims 23, 33, 35 and 36. Claims 23, 25-28, 30 and 32-37 will be examined.

2. Applicants' amendments and the Declaration of Dr. Koichi Hasegawa filed November 13, 2009 were sufficient to overcome all of the previously presented claim rejections and objections. Claims 23, 25-28, 30 and 32-35 are allowed.

3. Amendment to claim 36 resulted in the claim not being further limiting with respect to claim 32, and further lacking enablement with respect to granulocytopenias caused by an agent other than vesnarinone. Therefore this office action presents new grounds for rejection necessitated by amendment.

Claim Objections

4. Claims 36 and 37 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 36 is drawn to a method for examination of a subject for the risk of developing granulocytopenia comprising the method of claim 32. However, claim 32 is drawn to assessing the risk of vesnarinone-induced granulocytopenia, not any granulocytopenia, therefore claim 36 does not further limit claim 32.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

> with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 36 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for assessing the risk of vesnarinone-induced granulocytopenia based on the presence of polymorphisms in the human IRS2 gene, does not reasonably provide enablement for assessing the risk of any granulocytopenia based on detection of IRS2 polymorphisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 36 and 37 are broadly drawn to methods of assessing the risk of granulocytopenia by detecting a polymorphism of the human IRS2 receptor. However, as will be further discussed, there is no support in the specification and prior art for methods. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has a single working example in which subjects taking vesnarinone were examined for the presence of granulocytopenia associated with the drug and for polymorphisms in the IRS2 gene. Six polymorphisms, listed in Tables 1-6, were found to be significantly associated with the onset of granulocytopenia. No other patients subject to other therapeutic regimens were examined for polymorphisms in the IRS2 gene and their possible association with granulocytopenia.

Guidance in the Specification.

The specification provides no evidence that the disclosed six polymorphisms in the IRS2 would be indicative of the risk for granulocytopenia in patients taking drugs or drug combinations other than vesnarinone.

The unpredictability of the art and the state of the art

No other references were found teaching or suggesting an association between granulocytopenia caused by any other drugs and IRS2 polymorphisms. However, three very recent references discuss a possible link between acquired granulocytopenia and polymorphisms in other genes. For example, Berliner et al. (Hematology, vol. 2004, pp. 63-79, 2004; previously cited) discloses that in case of clozapine, tumor necrosis factor polymorphisms may play a role in the development of neutropenia (page 71, last two paragraphs; page 72, paragraphs 1-2 and Table 4).

Sugiyama et al. (J. Clin. Oncol., vol. 25, pp. 32-42, 2007; previously cited) examined the link between neutropenia caused by the anticancer drug gemcitabine in combination with carboplatin, cisplatin or fluorouracil, and polymorphisms in the cytidine deaminase (CDA) gene. They concluded that haplotype *3 was correlated with an increased risk for neutropenia in patients undergoing multiple drug therapy (Abstract; Table 2; page 37, fourth paragraph; Table 7; page 38, fourth paragraph).

Finally, Hahn et al. (Am. J. Health. Syst. Pharm., vol. 63, pp. 2211-2217, 2006; previously cited) teach that patients who are homozygous for the *28 allele of the uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) experience severe toxicity, including neutropenia (Abstract; page 2213, paragraphs 5-10; page 2214, first paragraph; Table 1).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to allow the use of polymorphisms in the IRS2 gene in the diagnosis of the risk of granulocytopenia caused by agents other than vesnarinone. First, all possible polymorphisms would have to be examined in the IRS2 gene, and then population studies with numbers of patients large enough to produce statistically significant results would have to be conducted for every drug and drug combination currently in use in clinical practice to treat any disease and correlated with the presence and/or absence of certain IRS2 polymorphisms. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the development of granulocytopenia in patients depends on a total genetic makeup of the patient as well as on the type of disease and drug being taken, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the teachings in the prior art

balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

7. Claims 23, 25-28, 30 and 32-35 are allowed. No reference were found teaching or suggesting claims 36 and 37, but they are rejected for reasons given above.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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